

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

TERRAZOLE

SB 950-045, Tolerance # 370
Chemical Code 580

July 8, 1987
Revised 1/19/90

I. DATA GAP STATUS

Chronic rat:	##	Data gap, inadequate study, possible adverse effect indicated
Chronic dog:		Data gap, inadequate study, no adverse effect indicated
Oncogenicity rat:	##	Data gap, inadequate study, possible adverse effects indicated
Oncogenicity mouse:		No data gap, possible adverse effect
Reproduction, rat:		Data gap, inadequate study, no adverse effect indicated
Teratology rat:		No data gap, no adverse effect
Teratology rabbit:		Data gap, inadequate study, possible adverse effect indicated

Gene mutation : No data gap, no adverse effect

Chromosome : No data gap, possible adverse effect

DNA damage : No data gap, possible adverse effect

Neurotox : Not required at this time

-----**Note, Toxicology**

one-liners are attached

indicates study on file but not reviewed

** indicates acceptable study

Bold face indicates possible adverse effect

File Name: T900119

Revised by J. Gee, 1/19/90.

Rectified with Library through 370-072, record number 070005 and 900000+.

II. Toxicology Summary

CHRONIC RAT

054 and 033 005186, "Toxicologic Study on the Effect of Adding Terrazole to the Diet of Rats for Periods of up to Two Years" (Medical College of Virginia, Dept. of Pharmacology 9-3-68). Terrazole, 95.3% purity; dietary dosing at 0 (corn oil), 10, 80, or 640 ppm given to 30/sex/group for 2 years; **Possible adverse effect: Incidence of renal lesions in males was dose related across all dose levels, testicular atrophy was dose related at mid and high dose.** UNACCEPTABLE due to no analysis of diet, no daily clinical exams, number of organ weights not clear, clinical biochemistry not done, no ophthalmological exam. (Wong, 3-19-85).

EPA 1-liner: MINIMUM, NOEL = 80 ppm.

044 016869. Partial duplicate of 005186.

CHRONIC DOG

054 and 032 005185, "Toxicologic Study on The Effect of Adding Terrazole to The Diet of Beagle Dogs for A Period of Two years" (Medical College of Virginia, Dept. of Pharmacology 8-5-68). Terrazole 95.3% purity, dogs were dosed in diet at 0, 10, 100, or 1000 ppm daily for 2 years, 4/sex/group; no adverse effects; NOEL = 100 ppm (decreased weight gain, elevated serum alkaline phosphatase and ChE); UNACCEPTABLE due to no diet analyses, no eye exam, missing tissues for histopathology, limited parameters for hematology, clinical chemistry. (Wong, 3/18/85, Gee, 1/17/90).

EPA 1-liner: MINIMUM, NOEL = 100 ppm.

044 016871. Partial duplicate of 005185.

ONCOGENICITY, RAT

072 070005, "Oncogenicity Study in Rats with Terrazole Technical" (Hazleton Laboratories Inc., HLA Study no. 798-210, 9/9/88). Terrazole technical, 98.8%, administered in the feed at concentrations of 0, 100, 640 or 1280 ppm to 50 Crl:CD*BR albino rats/sex/group for 104 weeks. Not yet reviewed by a toxicologist.

067 050820. Protocol for 070005.

055 035529, "Carcinogenicity Study with Echlomezole (F-2424) in Rats" (Shizuoka College of Pharmaceutical Sciences, Dept. of Pharmacology project no. 798-210). Groups of 58/sex fed test compound in diet at 0, 160, 320, 640, or 1280 ppm up to 80 weeks. UNACCEPTABLE. Procedures not described in sufficient detail for review, excessive mortality (up to 98%), no neoplasias. (Apostolou, 10-8-85).

No EPA 1-liner.

ONCOGENICITY, MOUSE

**** 046 to 053 and 067; 035516 to 035526 and 050829,** "Terrazole 18-Month Oncogenic Bioassay in CD-1 Mice: final report" (College of Medicine at Howard University Report no: 3543 5-81). Fifty-four to 68 mice per sex were given Terrazole (97.7%) at dietary concentrations of 0, 320, 640, or 1280 ppm for up to 18 months, with interim sacrifices at 6 and 12 months. **Dose related trends in pulmonary adenomas and carcinomas and total animals with tumors in both sexes.** Marginally ACCEPTABLE. Initially reviewed by Apostolou, 10-7-85 as unacceptable with no adverse effects indicated. Re-reviewed by J Carlisle, 7-6-87. Additional information (067) led to change in status to acceptable with possible adverse effects.

EPA 1-liner: SUPPLEMENTARY, oncogenic NOEL > 1280 ppm (HDT). Interpretive problems due to inconsistent timing and non-random assignment of animals to test groups. Kidney weights decreased in males at all treatment levels.

Note: In a recent comparison of EPA and CDFA data gaps, mouse oncogenicity was not listed as one of the differences so EPA's current position is not known. Gee, 1/19/90.

044 016872. Journal abstract of 035516.

069 063957. Supplement for 050829.

069 063956. Uniroyal response to CDFA re-review (adverse effects) of 035516.

REPRODUCTION, RAT

034 005187, "Three Generation Reproduction Study on Rats Receiving Terrazole in Their Diet", (Medical College of Virginia, Dept. of Pharmacology, 5-20-68). Terrazole, 95.3%, three generations of Charles River Sprague Dawley rats, 20/sex/group given 0, 10, 80, or 640 ppm test article in diet, females mated with a different male after 7 days of mating if necessary;

No adverse effects; UNACCEPTABLE due to insufficient histopathology, no analysis of diets, no indication of body weight other than at mating and weaning, no clinical observation data, no necropsy data. (Wong, 3/22/85; J. Parker, 10/28/85).

EPA 1-liner: MINIMUM, 80 ppm < NOEL < 640 ppm.

056 035530. Summary tables for 005187.

TERATOLOGY RAT

** 021 and 058 035533, "Teratology Study in Rats" (International Research and Development Corporation, 5-27-82 Report no: 397-035). Terrazole technical, 95%; Doses administered by gavage on days 6-19 of gestation, 25/group, at 0 (corn oil vehicle), 10, 30, or 75 mg/kg/day; Maternal toxicity at 75 mg/kg, 5/25 deaths, cause not determined, increase in clinical observations, decrease in body weight gain, Maternal NOEL = 30 mg/kg/day. Significant decrease in fetal weight, Developmental NOEL = 30 mg/kg/day. No adverse effects. Initially reviewed as acceptable (Wong, 3-20-85). Re-review considered this report unacceptable but upgradeable with description and results of dosing suspension analyses and individual data. (J. Parker, 10-21-85). In the process of replying to EPA on the difference in review of this study, the deficiencies were re-examined. The dosing analyses and the individual maternal and fetal data were indeed in the report as cited by EPA. The study was upgraded to ACCEPTABLE status. (J. Gee, 1/18/90).

EPA 1-liner: MINIMUM, teratogenic NOEL > 75 mg/kg/day; maternal NOEL = 30 mg/kg/day (Mortality, reduced body weight and body weight gain); fetotoxic NOEL = 30 mg/kg/day (reduced fetal weight, increased of delay ossification in sternebrae).

044 016874. Summary report of 035533.

012 947169, "Studies on The Teratogenicity of F2424 in Rats", (Nagoya Hoken Eisei University, Nagoya, Japan 11/30/81). Test article purity not given, 20 rats/group dosed orally by gavage on gestation days 7 to 16 at 0 (0.5% tragacanth), 0.4, 2.0, 10 mg/kg; UNACCEPTABLE; insufficient data to assess; no report of daily observations, no overt maternal toxicity, skeletal anomaly table not complete, high dose litter data not complete. (Wong, 3/21/85).

No EPA 1-liner.

044 016875. Partial report of 947169.

057 035531. Duplicate of 947169, but is missing table 18 (pup survival) and photos of skeletal preps).

012 and 057 035532, "Report to Olin Corporation Teratogenic Study with Terrazole in Albino Rats", (IBT Report no: 8533-10590, 6-78). Terrazole 97.7%, dose groups of 18 to 24 pregnant rats with 0(corn oil), 5, 15, 50, or 150 mg/kg on day 6 to 15 of gestation; study considered core supplementary by EPA. UNACCEPTABLE. (Wong, 3/21/85).

EPA 1-liner: SUPPLEMENTARY, teratogenic NOEL > 150 mg/kg (HDT); fetotoxic NOEL > 150 mg/kg (HDT).

TERATOLOGY RABBIT

058 and 008 035534, "Teratologic Evaluation of Terrazole Technical in Dutch-belted Rabbits (with protocol)", (Food and Drug Research Labs, Waverly, NY, report no. 5845 5-22-79). No purity given; administered to 14 to 17 dams by gavage on day 6 - 18 of gestation at 0, 1.7, 5.0, 15, or 45 mg/kg/day; at 45 mg/kg/day observed decreased maternal weight and maternal mortality (3/17), Maternal NOEL = 15 mg/kg/day. At 45 mg/kg/day, there was decreased live litter size, fetal weight and pup survival (24 hr), increased resorptions and malformations;

Developmental NOEL = 15 mg/kg/day; **Possible adverse effects indicated**, even though the NOELs are equivalent, the developmental effects are quite marked (total resorptions = 31 in the high dose compared to 7 in the control, 24 hour survival of 80% in the high dose compared to 99% in control). There is an increased incidence of malformations in the high dose which are not clearly described and may be of a serious nature ("tail defects, hind limbs underdeveloped and hind legs crossed"). Initially reviewed as acceptable (Wong, 3/20/85). Re-review found study to be UNACCEPTABLE but UPGRADEABLE with analysis of dose solution, individual data for fetal exams, maternal clinical observations and necropsy. (Reviewed by J. Parker, 10/25/85).

EPA 1-liner: GUIDELINE, fetotoxic NOEL = 15 mg/kg (decreased # of live fetuses/dam, significantly increased % of dams w/ resorbed fetuses as well as entirely resorbed litters, significantly reduced fetal weights, and neo-natal survival); teratogenic NOEL = 45 mg/kg (increase in % of litters w/ missing sternebrae and tail defect, increased frequency of crossed hind legs and open eyes).

044 016873. Abstract of 035534.

GENE MUTATION

059 035539, "In Vitro Gene Mutation Assay (HGPRT Locus) In Cultured Chinese Hamster Ovary (CHO) Cells on Terrazole, Batch 79-02-B" (Bioassay Systems report no. 10626, 11/10/81). Terrazole, 99.0% purity; zero to 0.008% tested with and without Aroclor-induced rat liver S9 activation; no adverse effects. no increase in mutation frequency; UNACCEPTABLE due to no confirming repeat experiment. (J. Gee,10-22-85).

EPA 1-liner: No core grade, No mutagenicity at doses as high as 0.005% in the culture medium w/S-9 fraction or 0.008% w/o S-9. Study done in duplicate instead of triplicate in a deviation from GeneTox recommendations.

044 016866 and 044 016864. Fragments of report 035539.

059 035535, "Evaluation of Terrazole for Mutagenic Effects in Bacterial Test Systems (with Salmonella typhimurium and Escherichia coli" (Pennsylvania State University 10-77 sponsor report no: 1072). Terrazole technical, 95.6% pure; zero to 2500 ug/plate or disc; no evidence of mutagenicity with either assay method or bacterium; UNACCEPTABLE due to no positive control data. (J. Gee, 10-21-85).

No EPA 1-liner.

044 038508. Brief summary of 035535.

059 035536, "Salmonella/Microsome Mutagenesis Assay on Terrazole" (Bioassay Systems 11-2-81, sponsor report no: 3719). Terrazole, technical grade 99.0% purity; 5 concentrations of zero to 2.0 ul/plate, TA98 and TA100; no evidence of mutagenicity reported. UNACCEPTABLE: used only 2 strains, no individual data. (J. Gee, 10-21-85).

EPA 1-liner: No core grade, Marginal increase of revertants at 0.06 ug/ml in TA100 without microsomal activation. Highest 2 doses toxic, no growth. Results reported only for strains TA100 and TA98. Study judged to be incomplete.

044 016867. Brief summary of 035536.

Summary: Although each individual study was found unacceptable due to flaws in the design or in reporting of data, CDFA believes collectively they provide sufficient data to determine that there is not an adverse effect.

CHROMOSOME

** 059 035538, "In Vitro Sister Chromatid Exchange Assay On Terrazole - Chinese Hamster Cells" (Bioassay Systems 1-82). Terrazole; cells exposed to 5 concentrations from 0.001 to 0.005 % with and without rat liver S9 activation; **possible adverse effect:** increase in SCE's without metabolic activation; ACCEPTABLE. (J. Gee, 10-22-85).

EPA 1-liner: No core grade, There were significantly increased numbers of sister chromatid exchanges in CHO cells grown in medium containing 100, 200, 300, 400, or 500 ug/ml. The increases in SCE's were observed only in cultures exposed to nonactivated terrazole .

044 016865. Brief summary of 035538.

** 059 035537, "Effects of Terrazole on the in vitro Induction of Sister Chromatid Exchanges and Chromosomal Aberrations in Chinese Hamster Ovary Cells" (Bioassay Systems Corp 6-4-82). Terrazole technical with and without activation, doses of 0 - 0.006%; **possible adverse effect:** increased chromosomal aberrations without activation; confirmed results of 035538; ACCEPTABLE. (J. Gee, 10-21-85).

EPA 1-liner: No core grade, Increased the frequency of chromosome breaks at concentration of 500 and 600 ug/ml. Increased number of sister chromatid exchanges at concentration of 300, 400, 500, or 600 ug/ml. Chromosomal aberrations were observed to occur with or without metabolic activation. SCE's were seen without metabolic activation.

044 016864. Partial duplicate of 035537. Table of contents and pages 1-6 are missing.

DNA DAMAGE

** 059 041953, "Effects of Terrazole on the in vitro Induction of Sister Chromatid Exchanges of Chromosomal Aberrations in Chinese Hamster Ovary Cells (Sister Chromatid Exchange Assay)" (Bioassay Systems 6-4-82) Technical Terrazole 99.0% pure; treat without activation, 5 concentrations from 0.001 to 0.005 % for 27 - 28 hours; **possible adverse effect:** increase in aberrations and SCE's; ACCEPTABLE. (J. Gee, 10-21-85).

044 016868 "Summary Evaluation of Terrazole for Mutagenic Effects in Bacterial Test Systems-DNA Repair" (Pennsylvania State University Report no: 1072-76) diffusion test with E. coli. UNACCEPTABLE, insufficient data to assess: brief summary. (Wong, 3/22/85).

NEUROTOXICITY

Not required at this time.